LIVER FUNCTION AND COLLATERAL ARTERIAL CIRCULATION OF THE LONG SURVIVORS (DOGS) FOLLOWING INTERRUPTION OF THE HEPATIC ARTERY

AUTHOR(S):

KOSHIBA, TAKAO

原　　著

LIVER FUNCTION AND COLLATERAL ARTERIAL CIRCULATION OF THE LONG SURVIVORS (DOGS) FOLLOWING INTERRUPTION OF THE HEPATIC ARTERY

by

TAKAO KOSHIBA

From the 1 st Surgical Division Kyoto University Medical School
(Director : Prof. Dr. CHISATO ARAKI)

Received for Publication Sep. 7, 1963

Contents

I. INTRODUCTION

The fact that about 80 per cent of the dogs whose arteries entering the liver are interrupted, expire due to massive liver necrosis, has been acknowledged by HABERER[1] and many others. In 1949, MARKOWITZ, RAPPAPORT and SCOTT[2] reported that the mortality rate of hepatic artery ligation in dogs was remarkably decreased by postoperative administration of penicillin. In 1950, GRANT, FITTS[2] and RAVDIN[4] also reported the similar results.

While extensive hepatic necrosis develops in dogs dying of ligation of the hepatic artery, no such violent change can be observed in the liver of the dogs surviving the procedure. Regarding the mechanism of the onset of the fatal liver necrosis, HONJO and his collaborates[5] have made an extensive study and insisted that the disturbance of the intrahepatic portal circulation induced by the interruption of the hepatic artery should play primarily an important role in the development of such a necrosis.

On the other hand, there has been a great number of investigators who believe that in dogs, which survived the procedure, the arterial collateral circulation develops entering the liver. GRINDLAY, MANN and BOLLMAN[6][7] have reported on the arterial system communicating the diaphragm with the liver. MARKOWITZ, RAPPAPORT and EZE[8] asserted that the cause of decrease in the mortality rate by the postoperative use of penicillin should be attributed to the development of adequate arterial collaterals which is achieved while penicillin is preventing the development of hepatic necrosis. LAUFMAN[9] and WITTER[10] demonstrated the existence of small arteries in the hepatoduodenal ligament and in the hepatorenal ligament as well as in the diaphragm, which are capable of communicating with those of the liver, and proposed that the more such arterial pathways may be found in the dogs, the longer they survived the operation. Furthermore, Popper and his co-workers[11] emphasized that so long as the arterial collaterals are sufficiently retained after ligation of the hepatic artery, the animals may be able to survive without being administered with antibiotics, whereas death would be unavoidable no matter how much of antibiotics may be administered, once these collaterals are completely interrupted.

Against these views, TANTURI and others[12], denying the existence of collateral pathways from the diaphragm to the liver, strongly asserted that even if there existed such small vessels, their existence alone would not be sufficient to explain animals' survival after the hepatic artery ligation.

URABE[13], in our laboratory, was not able to find roentgenologically any effective collaterals within two weeks after interruption of the hepatic artery. ISHIGURO[14], also in our laboratory, studied development of the arterial collaterals after interruption of the hepatic artery and concluded, "Although it would be difficult to interrupt completely all of the arterial blood flow into the liver, almost complete interruption of such blood flow might be practically achieved by the ligation of the common hepatic, gastroduodenal and right gastric arteries, and the remaining filamentous arterial branches, which may communicate with the hepatic vessels, are never sufficient to justify animals' survival. Besides, even when the right gastric artery and other collaterals are preserved on purpose, that is, when only both of the gastroduodenal and common hepatic arteries are ligated, no significant difference will be brought in the mortality rate. The arterial distributions other than those from the two channels of the common hepatic and gastroduodenal arteries can never be the factors which affect the life of dogs."

It would be an interesting subject to study in what manner develop these arterial collaterals communicating with the intrahepatic arterial system in the dogs which survive for a long period of time after interruption of the hepatic artery and what correlation exists between these collateral circulations and liver function.

Ⅱ. METHODS

1. Experimental Materials and Operative Procedures

A. Experimental Materials

Healthy adult mongrel dogs, 5.4kg to 18.5kg of body weight, were employed.

B. Operative Procedures

Laparotomy was performed by an upper midline incision under intravenous nembutal anesthesia. For the purpose of interrupting the flow of arterial blood at the hilum of the liver as thoroughly as possible, the extrahepatic bile duct and the portal vein which run in the hepatoduodenal ligament were deliberately isolated from their surrounding connective tissues, then together with these connective tissues, the common hepatic, the gastroduodenal and the right gastric arteries were doubly ligated and cut. In some cases, cholecystectomy was concurrently carried out. After the operation, penicillin of one to three hundred thousand units was injected intraperitoneally or intramuscularly.

2. Liver Function Tests and Examinations of Blood

In order to study the influence of hepatic arterial ligation on the liver, routinely the liver function of each dogs were examined before and after the operation extending over a certain period of time and blood examinations were also performed.

As for liver function tests, sublimate reaction, MEULENGRACHT'S icterus index, zinc sulphate test of KUNKEL, bromsulphalein test (B. S. P. test) and TAKATA'S reaction were carried out.

In bromsulphalein test, percentage of the dye retained in the serum was determined, 20 and 45 minutes after the injection of hepatosulphalein (5mg per kg body weight), respectively.

In TAKATA'S reaction, the concentration of the sublimate solution was raised up to 1.5% according to TSUCHIYA'S modified method[15] and determination was carried out after the materials were left in room temperature for 3 hours.

As for blood examinations, red blood cell count, concentration of hemoglobin (SAHLI'S method) and content of total serum protein were examined. In the last examination, an ATAGO'S serum-protein meter was used, and values were corrected depending upon the temperature.

3. Preparation of Plastic Cast Specimens

In order to observe precisely arterial collaterals of the dogs surviving the operation, plastic cast specimens were prepared. For comparative study, the same specimens of normal dogs were also prepared.

A. Extirpation of Raw Specimens

In an attempt not to miss any arterial branches to the liver, the specimen was extirpated over a sufficiently wide range, including the surrounding organs, as shown in Fig. 1.

Under intravenous nembutal anesthesia, laparotomy was carried out. The greater omentum was cut off along the greater curvature, leaving the gastroepiploic vessels to the stomach and the spleen was separated at its hilum and extirpated. The intestine was cut at the beginning of the jejunum and in order to preserve the draining area of the inferior pancreaticoduodenal artery which originates from the superior mesenteric artery, the other branches of the mesenteric arteries than the superior mesenteric artery were ligated and

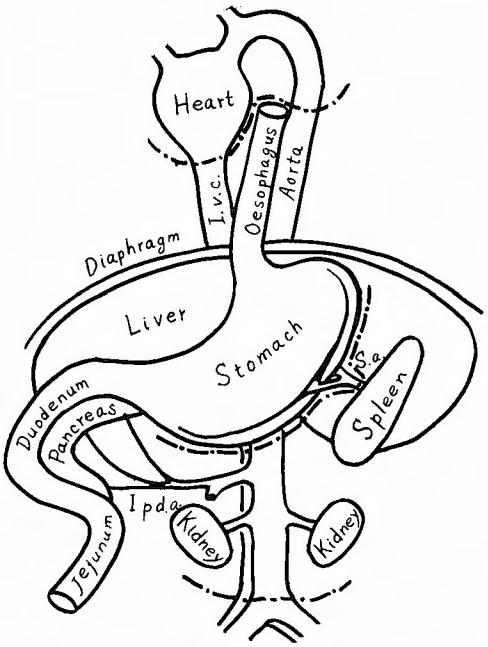


Fig. 1. Range of extirpation of the specimen.
I. v. c. : Inferior vena cava
S. a. : Splenic artery
I. p. d. a. : Inferior pancreaticoduodenal artery
..... : Borderline of extirpation

cut at the radix of the mesentery. Then the abdominal aorta was cut below the renal arteries whose branches might possibly anastomose with the intrahepatic arterial system. The inferior vena cava was ligated and cut at the same level as the aorta. Thoracotomy was finally carried out along the sternal margin, and the inferior vena cava was ligated and cut immediately below the sinus of the vena cava, and both the esophagus and the aorta were ligated and cut at the level of the lowest end of the aortic arch. Thus, inculding the both kidneys, the liver, esophagus, diaphragm, stomach, duodenum and the beginning part of the jejumum, the posterior mediastinum and retroperitoneum existing in these thoracoabdominal area together with the muscles attached to the spine were extirpated en bloc.

B. Irrigation

Prior to infusion of the plastics into the vascular system after extirpation of the organ, thorough irrigation was carried out to make the infusion complete and easier. For irrigation, a squirt-like glass tube was inserted into and fixed at three points to the vessels in the way as described in the below. To the glass tube, the instrument devised by IKEGAMI[16] and an irrigation apparatus made by the author (Fig. 2) were connected.

For arterial system, the infusion was carried out from the cut end of the aortic arch normogradely, and for portal system, the infusion was performed at the hilum of the liver normogradely. As for the inferior vena cava and the hepatic vein, the infusion was carried out retrogradely from the cut stump of the sinus of vena cava.

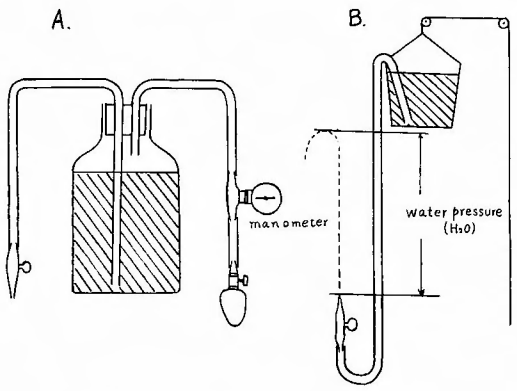


Fig. 2. Irrigation apparatus.
A : By IKEGAMI
B : Made by the auther

In performing the irrigation, oozing points were strictly ligated. Clean water was used for the irrigation and the pressure of irrigation was adjusted at about 200mm Hg for artery and 10mm Hg for hepatic and portal vein, approximating the experimental condition to normal physiological one. Irrigation was performed slowly and deliberately so that thrombus may be prevented and the wall of the capillary vessels may not be injured.

C. Infusion of Plastics

Following irrigation, the plastics was infused into the arterial system at first, and then into the portal system and in the hepatic venous system lastly.

i) *Preparation of Plastics for Infusion, and Method of Infusion*

The plastics used here was that produced by MIKI Plastic Chemical Co.

The monomeric methyl methacrylate of low viscosity was mixed homogenously with an appropriate amount of fine particles of pigment as coloring dyestuff and of benzoyl peroxide as a stimulant of polymerization. Then the intermediate methyl methacrylate polymer of high viscosity and the mixture aforementioned were mixed thoroughly at a proportion of 3-5 : 1. Immediately after, the mixture became viscous like millet jelly, it was sucked in a syringe which was connected to a glass tube placed at each vessel and then infusion was carried out with care so that no excessive pressure may be applied. The infusion was continued until the pigment appeared slightly visible on the surface of the liver.

In order to make the observation of the specimen easier, the arterial infusion was performed with red-colored plastics, while the portal system and hepatic venous system were infused with blue and yellow or light green-colored plastics respectively.

After completion of the infusion, the specimens were immersed in water until the polymerization was accomplished, in order to avoid the effect of polymerizing heat and change of the shape after polymerization.

ii) *Corrosion of Tissues and Washing of Specimens*

Following completion of polymerization, the specimen was immersed in 30 to 40 per cent caustic soda solution for several days to make the tissues corroded up to their innermost part. Then the specimen, thus corroded, was floated deliberately in water and un-

necessary tissues were washed away by pouring water. After washing away the corroded tisssues, a beautiful plastic cast preparation of vascular nets of the liver and its surrounding tissues were obtained. Then the specimen was dried up and carefully preserved for subsequent study.

Ⅲ. Results

1. Operative Mortality

One hundred and twenty healthy mongrel dogs were used. Seven out of them were used for normal control and 113 dogs were subjected to hepatic arterial interruption.

All the dogs were administered with penicillin after the operation, but as shown in Table 1, about a half of them or 56 cases expired within two postoperative weeks as a result of the direct effects of the operation. The mortality was as high as 49.5 per cent. The high mortality may be due to the great operative aggression in the hilar region at the time of hepatic arteril interruption.

Table 1. Operative Mortality Rate.

		No. of Dogs	Mortality Rate %	
Total Cases		113		
Survivals		22		
Missing		5		
Deaths Due to Other Causes	Distemper	22	19.5	
	Other Unknown Causes	8	7.1	
Deaths Due to Operation	Liver Necrosis	42	37.2	49.5
	Bile Peritonitis	14	12.3	

Of 57 cases surviving the operation, 22 cases suffered from distemper and expired within 2 postoperative months. Eight other cases died of malnutrition or of other unknown causes and 5 cases ran away in the course of aftercare and are still missing. The remaining 22 cases survived for 2 to 18 months after the operation and were provided for the examination of the collateral arterial circulation.

2. Liver Function and Blood Findings

A. Preoperative Values

In order to find out the normal values in the dogs, a majority of the experimental dogs were subjected to the examination prior to the operation.

i) *Sublimate Reaction* (Fig. 3)

Ninety-three cases were subjected to sublimate reaction. The amount of the reagent required for flocculation of the serum was 0.30 to 0.54 c.c. among which 0.35 to 0.54 c.c. were required in 88 cases or 95.0 per cent of the cases. 0.35 c.c. and more of sublimate reagent will be assumed to be the normal values.

ii) *MEULENGACHT'S Icterus Index* (Fig. 4)

Of 90 cases, icterus index was shown between 2 and 10. Indices 2 to 6 were shown

Fig. 3, 4, 5, 6, 7, 8, 9 and 10. Preoperative examinations of the liver functions and the blood

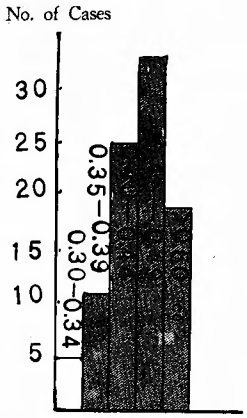


Fig. 3. Sublimate reaction in 93 normal dogs

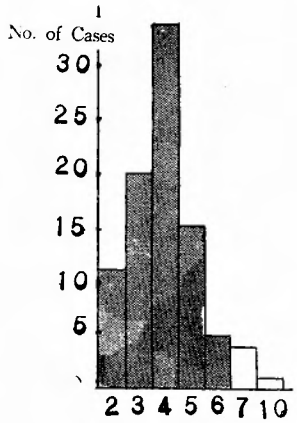


Fig. 4. MEULENGRACHT icterus index in 90 normal dogs

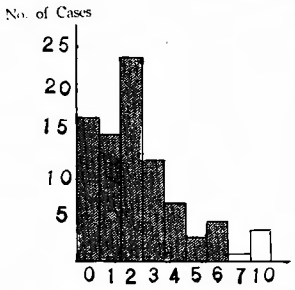


Fig. 5. KUNKEL'S Zinc sulphate test. in 88 normal dogs.

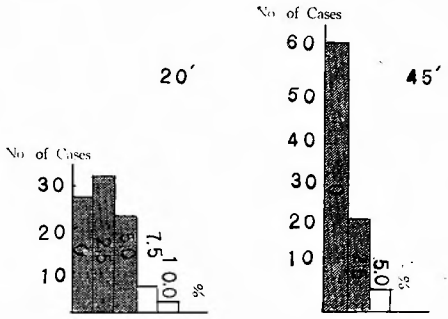


Fig. 6. Bromsulphalein test. in 91 normal dogs

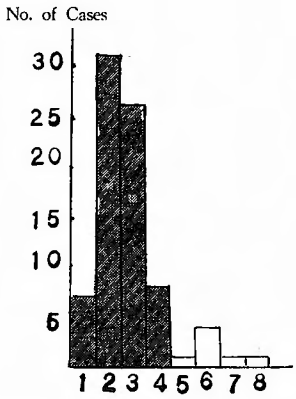


Fig. 7. TAKATA'S reaction in 79 normal dogs.

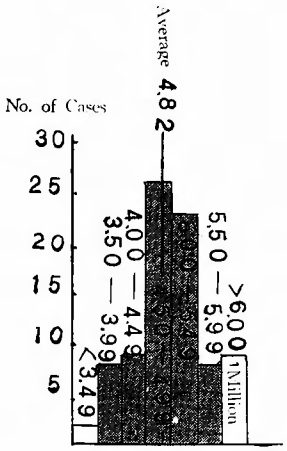


Fig. 8. Red blood cell count. in 85 normal dogs.

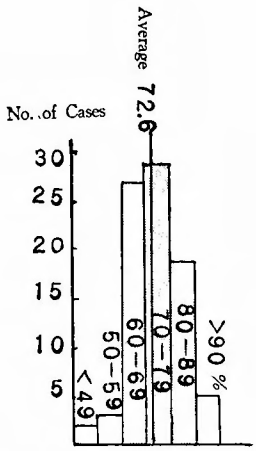


Fig. 9. Hemoglobin concentration (SAHLI's method) in 85 normal dogs.

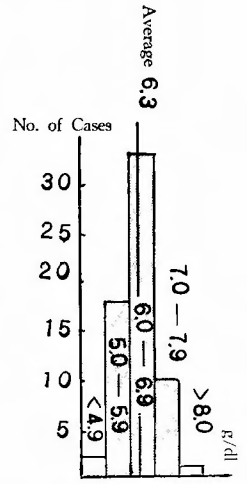


Fig. 10. Total serum portein in 64 normal dogs.

in 85 cases, or 95.5 per cent of the cases. It was assumed that the index up to 6 would be normal.

iii) *KUNKEL'S Zinc Sulphate Test* (Fig. 5)

The test was carried out in 88 cases, of which 83 cases or 94.3 per cent of the cases had the values of 0 to 6 units, which were considered normal value.

iv) *Bromsulphalein Test* (B.S.P. Test) (Fig. 6)

Twenty minutes after injection of hepatosulphalein (DAIICHI SEIYAKU Co., Ltd.), the concentration of dye retained in serum was 0 to 5 per cent in 82 cases or 90.1 per cent of the total 91 cases subjected to the test. The concentration more than 7.5 per cent was demonstrated in only 9 cases or 9.9 per cent of the total cases.

The concentration of dye in serum 45 minutes after injection was between 0 and 2.5 per cent in 85 cases or 93.4 per cent of the total cases. The value more than 5 per cent was seen in only 6 cases or 6.6 per cent of the cases. The normal value 20 minutes after the injection may be safely considered to be 5.0 per cent and that after 45 minutes 2.5 per cent at most.

v) *TAKATA'S Reaction* (Fig. 7)

Seventy nine cases were subjected to the test. The number of test tube in which flocculation was seen was 1 to 4 in 72 cases or 91.1 per cent of the total cases. It was considered that more than 5 test tube which showed flocculation was abnormal.

vi) *Red Blood Cell Count* (Fig. 8)

The examination was performed in 85 cases. The number of erythrocyte was distributed from 1.56 million to 6.5 million, 4.82 million on the average. Even if the cases with anemia and polycytemia were avoided, the normal range of red blood cell count in dogs seemed to be broad. This may be due to the nutritional condition or the existence of parasites. Considering the whole aspect of the distribution of erythrocyte number in

dogs, 5 million ± 1 million could be taken as normal range.

vii) *Hemoglobin Content* (SAHLI's Method) (Fig. 9)

Contrasted with human begings, dogs were generally more hypochromic. Average value of 85 cases was 72.6 per cent. In considering the interrelationship with the red blood cell count, 75 ± 15 per cent may be evaluated to be normal value.

viii) *Total Serum Protein Content* (Fig. 10)

The measurement was carried out for 64 cases. The average value was 6.3g per dl. In 61 cases out of 64, or 95.3 per cent the value was between 5.0 to 7.9g per dl. Six point five ± one point five g per dl may be considered to be approximately normal value.

B. Postoperative Values

Most of the dogs, surviving the operation, were subjected regularly to the same examination as before the operation, and the influence of hepatic arterial interruption upon liver function, red blood cell count and serum protein content were studied. In the liver function tests, the value beyond the normal range was considered abnormal and those cases revealing abnormalities in more than two different examinations were considered as dogs with impaired liver function. From this point of view 14 cases out of 44 revealed impaired liver function. Of these 14 cases, 8 cases (No. 36, 7, 68, 89, 99, 107, 10, 27) were not affected evidently by interruption of the hepatic artery but expired by other causes, except 1 dog (No. 36) which expired on the 12th postoperative day with bile peritonitis due to perforation of the gallbladder. Three dogs (No.7, 68, 89) expired 2 weeks after the operation and 1 dog (No. 107) died 4 weeks after the operation of impaired liver function due to distemper. Three dogs (No. 99, 10, 27) expired 4 weeks, 6 weeks, and 2 months after the operation, respectively, by the deterioration of the liver function due

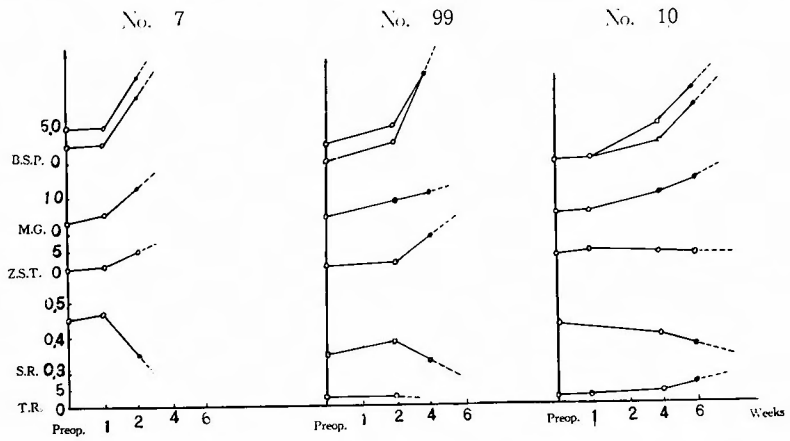


Fig. 11. Three cases expired from the impaired liver function due to other causes than the operation.
T. R. : TAKATA's reaction S. R. : Sublimate reaction
Z. S. T. : KUNKEL's zinc sulphate test
M. G. : MEULENGRACHT icterus index
B. S. P. : Bromsulphalein test
The white spot shows normal value.
The black spot shows abnormal value.

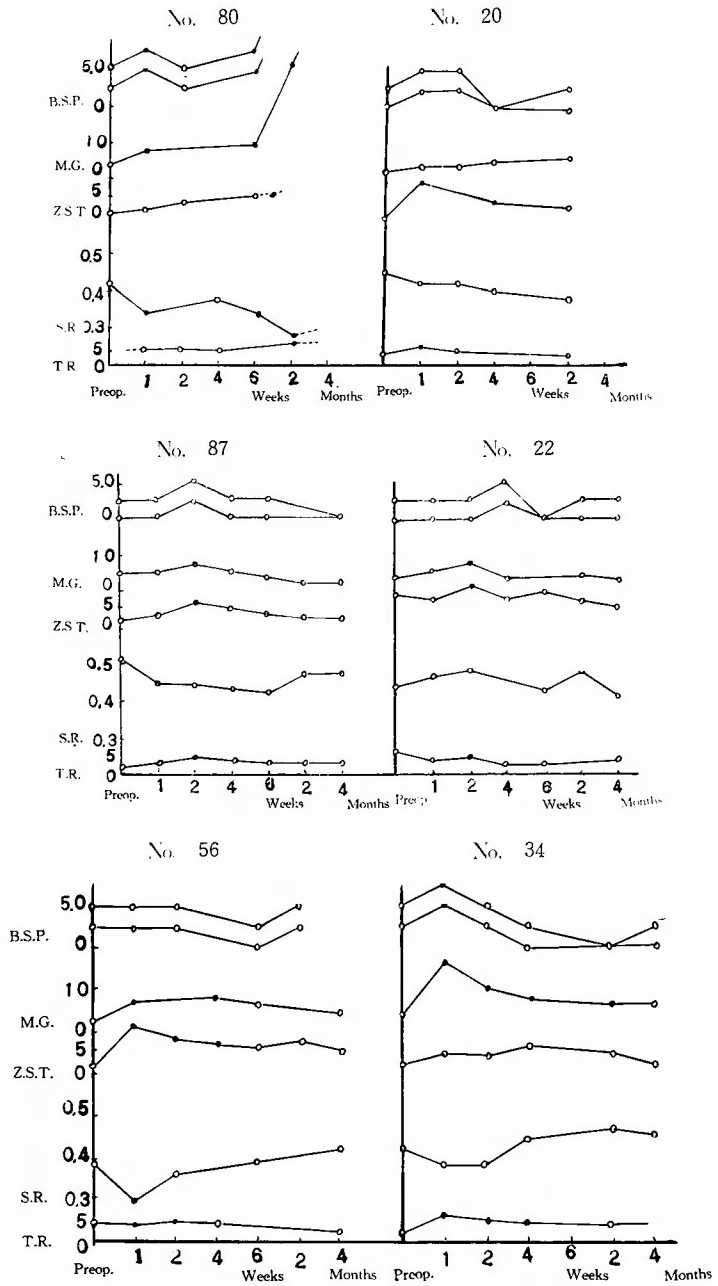


Fig. 12. Six cases of survival whose liver functions were impaired by the interruption of the hepatic artery.

to unknown cause at the time when the direct influence of hepatic artery ligation on liver function could be neglected. (Fig. 11) In the remainder of 6 cases (No. 80, 20, 87, 22, 56, 34), liver function was slightly impaired for a week or two after the operation. (Fig. 12)

No close correlation could be found between each examination, while MEULENGRACHT's icterus index and B.S.P. test were found to be most sensitive and these two tests could serve as useful indices of liver impairment.

On the whole, the results of the liver function tests showed merely slight fluctuation within the normal range in almost all cases after the operation. Of 44 cases, only 6 cases (13.6 per cent) showed a slight and temporary impairment, thus leading to the assumption that there was practically no effect to be observed after hepatic arterial interruption.

On the number of red blood cell, hemoglobin content and total serum protein content, influence of operation was distinctly apparent.

The values of these tests decreased generally after the operation and reached the lowest by 2 weeks and recovered gradually in the 4th week. In the 2nd to 3rd month after the operation these values returned to their preoperative ones in most cases. (Fig. 13)

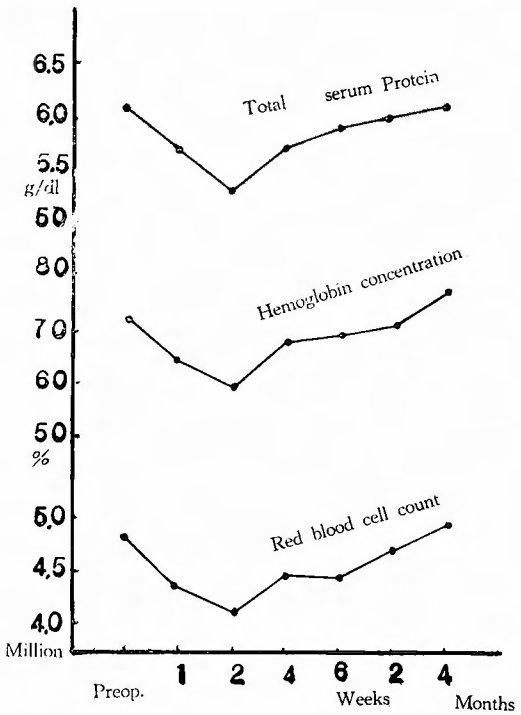


Fig. 13. Red cell count, hemoglobin concentration and content of total serum protein after the hepatic arterial interruption. (Average of 14 cases)

3. Findings of Plastic Cast Specimens

A. Arterial System of the Liver and of its Neighbouring Organs in Normal Dogs.

i) *Arteries Near the Hilum of the Liver*

It is deemed necessary to decribe in detail the arterial system in the neighbourhood of the hilum of the liver, the importance of which is recognized as one of the postoperative collaterials.

The common hepatic artery, originating from celiac axis forms an arch at the hilum of the liver and branches the proper hepatic arteries towards the liver and bifurcates into

the gastroduodenal artery and the right gastric artery. The right gastric artery, making an anastomosis with the left gastric artery, forms the gastric coronary artery along the lesser curvature of the stomach and sends filamentous branches to the hepatogastric liga-

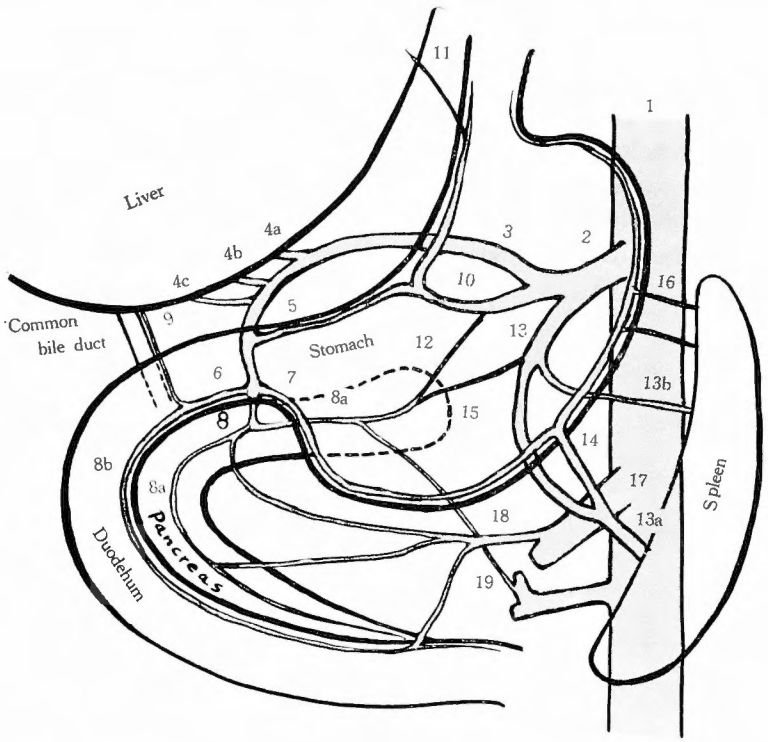


Fig. 14. Arterial system distributing to the organs neighbouring the hilums of the liver in normal dog.

1 : Abdominal aorta
2 : Celiac axis
3 : Common hepatic artery
4 : Proper hepatic artery
a : Left main branch
b : Middle main branch
c . Right main branch
5 : Right gastric artery
6 : Gastroduodenal artery
7 : Right gastroepiploic artery
8 : Superior pancreaticoduodenal artery
a, a' : Branch to the pancreas
b : Branch to the duodenum
9 : Cholecystic artery
10 : Left gastric artery
11 : Small branch of the left gstric artery which enter the liver.
12 : Small branch of the left gastric artery which communicates with the pancreatic branch. (8 a')
13 : Splenic artery a : Main branch b : accessory branch
14 : Left gastroepiploic artery
15 : Small branch of teh splenic artery which communicate with the pancreatic branch. (8 a')
16 : Branch of the left gastroepiploic artery which flow into the spleen.
17 : Superior mesenteric artery
18 : Inferior pancreaticoduodenal artery
19 : Small branch of the right inferior phrenic artery which anastomoses with the pancreatic branch (8 a')

ment. At the side of the greater curvature of the pylorus the gastroduodenal artery bifurcates into the right gastroepiploic artery and the superior pancreaticoduodenal artery. The former communicates with the left gastroepiploic artery which originates from the splenic artery and nourishes both the greater curvature of the stomach and the greater omentum. The main branch of the latter runs behind the duodenum to the pancreas and communicates with the inferior pancreaticoduodenal artery, which comes from the superior mesenteric artery, and is distributed to the duodenum and pancreas. A branch of the superior pancreaticoduodenal artery is distributed to the pylorus extending to the beginning part of the duodenum. A branch of the left gastric artery, or of the right inferior phrenic artery or of the splenic artery runs retroperitoneally to enter the pancreas and forms often anastomosis with the superior pancreaticoduodenal artery. (Fig. 14)

ii) *Intrahepatic Arteries*

The common hepatic artery branches into the right, left and middle proper hepatic arteries towards the hilum of the liver and is further ramified arborescently in the liver. The intrahepatic arterial system forms the so-called capsule of GLISSON and is distributed to each of the lobules, together with the intrahepatic portal and bile duct systems.

iii) *Inferior Phrenic Arteries*

The inferior phrenic artery usually comes from the abdominal aorta approximately in the middle point between the superior mesenteric artery and the renal artery as a pair of left and right. The left inferior phrenic artery ascends, sending small branches to the retroperitoneum and the lumbospinal muscles on the left side of the spine, to the neighborhood of the cardia of the stomach and the esophageal hiatus of the diaphragm and maintains a fine anastomosis with arterial system which is distributed in the stomach and esophagus.

It also forms an especially distinct anastomosis with a branch of the left gastric artery. It courses between the left inferior lobe and the caudate lobe of the liver and sends fine branches into the liver. (Fig. 15)

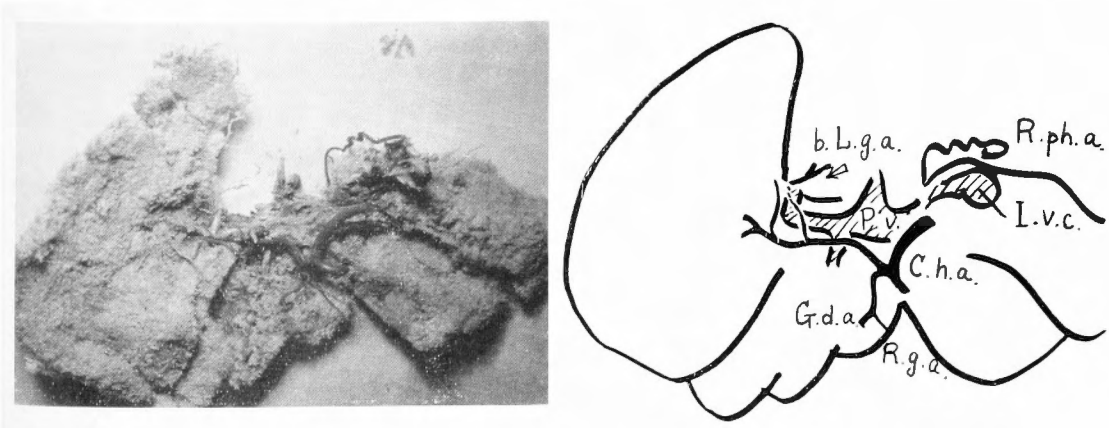


Fig. 15 A small branch of the left gastric artery anastomosing with the left inferior phrenic artery runs between the caudate lobe and the left inferior lobe and communicates with the left proper hepatic artery in normal dog.

Furthermore the main branch is ramified radially at a point where the left hepatic

vein joins the inferior vena and is distributed to the left half of the diaphragm.

The right inferior phrenic artery comes out from the opposite side of the left inferior phrenic artery, similarly runs upward, coursing approximately in parallel with the upper side of the inferior vena cava and letting out fine branches to the wall of this vein, forms a reticular anastomosis with the arteries in the stomach and esophagus at the right side of the cardia. Furthermore it sends out several fine branches which anastomose with those of the left inferior phrenic artery and is distributed to almost all area of the right half of the diaphragm.

As a variant of the inferior phrenic artery, it comes sometimes from the renal artery, from the superior mesenteric artery or from the celiac axis.

iv) *Other Arteries*

Although the renal artery is not usually related to the intrahepatic arterial system, it sometimes happens that fine branches from the right renal artery find their way in the right hepatorenal ligament and enter the liver.

The left gastroepiploic artery, a branch from the splenic artery, anastomoses near the cardia with the inferior phrenic, left gastric and esophageal arteries. A branch communicating with the superior pancreaticoduodenal artery comes out from the splenic artery as already mentioned in the above. The left gastroepiploic artery, however, does not apparently have any direct communication with the intrahepatic arteries.

Besides, there are arteries (the esophageal, superior phrenic and internal mammary arteries etc.) which, coming from and descending along the arcus aortae, anastomose with the inferior phrenic artery. There are also lumbar arteries which originate from the abdominal aorta. These, however, do not have any relation with the hepatic arterial system.

B. Findings of Arterial System Around the Liver in Experimental Dogs.

In 22 out of 24 cases of long survival, plastic cast specimens were prepared and the collateral arterial pathways were observed in detail over the period of 2 to 18 months after the operation.

i) *Gross Findings of Raw Specimens*

Prior to the preparation of plastic cast specimens, the extirpated specimens were macroscopically observed at the time of sacrifice.

At laparotomy, a strong adhesion was often noted between the operative wound and the margin of the liver or the greater omentum, and in a majority of cases, centering around the site of ligation, adhesion of a high degree was also noticed between the hilum of the liver and its surrounding organs, ---especially in the pyloric region and the beginning part of the duodenum. The liver generally showed normal gloss, tincture and consistence, while in many cases, peripheral region of the middle lobe and a part of the caudate lobe where hepatic necrosis easily develops, were seen to be roundly deformed with grayish brown discoloration showing an appearance of cicatric atrophy, frequently forming an adhesion with the diaphragm or the greater omentum.

ii) *Formation of Collateral Arterial Pathways in Plastic Cast Specimens.*

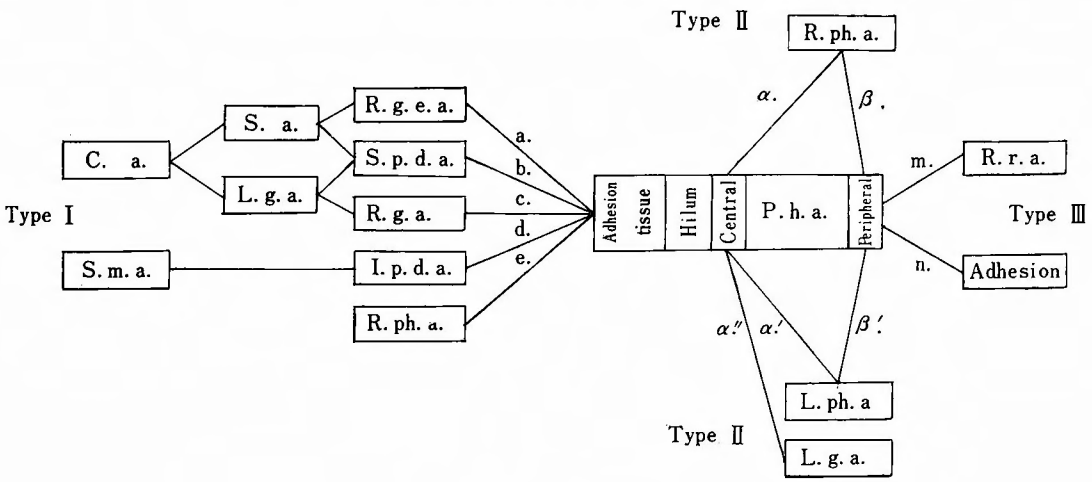
Although differences of survival period and individuality between each dog could not be avoided, in all of the 20 long survivals of 69 to 551 day, a distinct formation of collaterals, connecting the extrahepatic arterial system with the intrahepatic one were obser-

ved, moreover, intrahepatic arterial system was distributed in a way quite similar to that before the operation, corresponding to that of the portal system.

iii) *Classification of the Arterial Collateral Pathways Entering the Liver Parenchyma.*

Although the arterial collateral pathways entering the liver parenchyma are formed through various routes, these pathways could be classified into three types, (1) entering the liver from the hilum of the liver, (2) from the diaphragmatic surface of the liver, (3) from other collateral routes, which were nominated as type I, II and III, respectively (Table 2). Of these, Type I and II had the most potent and important collaterals. Fur-

Table 2. Schema of Various Kinds of Arterial Collateral Pathways.



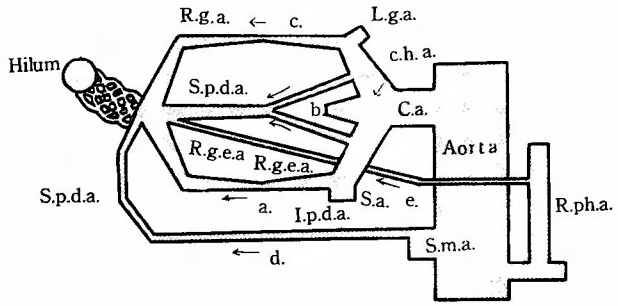


Fig. 16. Courses of the arterial collateral pathway of the type I.

C.a. : Celiac axis
C.h.a. : Common hepatic artery
L.g.a. : Left gastric artery
S.a. : Splenic artery
S.m.a. : Superior mesenteric artery
R.g.a. : Right gastric artery
S.p.d.a : Superior pancreaticoduodenal artery
I.p.d.a. : Inferior pancreaticoduodenal artery
R.g.e.a. : Right gastroepiploic artery
L.g.e.a. : Left gastroepiploic artery
R.ph.a. : Right inferior phrenic artery
L.ph.a. : Left inferior phrenic artery
R.r.a. : Right renal artery
P.h.a. : Proper hepatic artery

thermore, the collateral pathways of these three types could be subdivided according to their origin.

As for type I, which was considered as newly formed collaterals at the site of adhesion in the hilum, the collateral pathways were subdivided into five routes (a, b, c, d, e) as shown in Fig. 16.

The route a is the course which originates from the left gastroepiploic artery and enters the right gastroepiploic artery, passing through their anastomotic branches and finally runs towards the stump of the gastroduodenal artery retrogradely.

The route b branches off at the beginning part of the left gastric or splenic artery and communicates with the superior pancreaticoduodenal artery and lastly reaches the stump of the gastroduodenal artery.

The route c originates from the left gastric artery and reaches the stump of the right gastric artery passing through the gastric coronary artery.

The route d comes out from the inferior pancreaticoduodenal artery which originate from the superior mesenteric artery, passing through anastomotic branches and enters the superior pancreaticoduodenal artery and finally reaches the stump of the gastroduodenal artery.

The route e is the course which comes out from the right inferior phrenic artery and communicates with the beginning part of the superior pancreaticoduodenal artery and then reaches the stump of the gastroduodenal artery.

The collateral pathways of type II were subdivided into two groups of α and β. The route α is a course which communicates directly with either the right or the left proper hepatic artery passing either side of the caudate lobe.

The route β originates from the portion around the inferior vena cava and left hepatic vein and enters the parenchyma and reaches the peripheral part of the proper hepatic artery of the each lobe.

Of the former route, the pathway which comes out from the right inferior phrenic artery was designated as α, and the one from the left inferior phenic artery as α' and that from the branch of the left gastric artery as α''.

Of the latter course, the pathway which comes out from the right inferior phrenic artery was designated as β, and the one from the left inferior phrenic artery as β'. (Fig. 17)

The type III was subdivided into two groups of m and n.

The route m is fine branches originating from the right renal artery and enters the liver through the right hepatorenal ligament. The route n is the pathway entering the liver parenchyma through the adhesion outside of the hilum.

iv) *Findings in Each Collateral Pathway in the Plastic Cast Specimens.*

a. Around the hilum of the liver (Type I; a, b, c, d, e)

As described in the operative procedure, the interruption of the hepatic artery was performed by double ligation and division of three arteries, namely the common hepatic, gastroduodenal and right gastric arteries. The common hepatic artery was divided as close as possible to its origin, the celiac axis. Both the gastroduodenal and right gastric arteries were divided at each peripheral portion apart from the common hepatic artery.

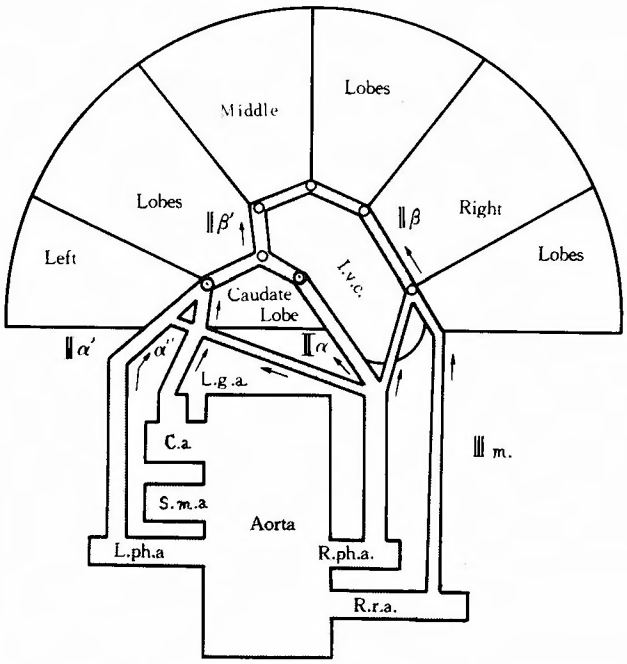


Fig. 17. Courses of the arterial collateral pathways of the type II and III m.

C.a. : Celiac axis
L.g.a. : Left gastric artery
S.m.a. : Superior mesenteric artery
R.ph.a. : Right inferior phrenic artery
L.ph.a. : Left inferior phrenic artery
I.v.c. : Inferior vena cava

Therefore, there exists an arcus of the common hepatic artery which branches the proper hepatic artery, at the hepatic side of the division.

Both stumps of each divided artery are not distant from, but close to each other and are fixed anatomically to the surrounding tissue. It is possible for both stumps of each artery to be drawn near easily to each other by postoperative adhesion at the hilum of the liver. Besides, the gastroduodenal artery and the right gastric artery have many anastomosis with the left gastroepiploic artery, the inferior pancreaticoduodenal artery and the left gastric artery in their peripheral portions and receive retrogradely sufficient arterial blood supply. It may be supposed that the collateral arterial circulation may be achieved very easily at the hilum of the liver.

In most cases, the adhesion took place at the hilum postoperatively and both the arterial stumps of hepatic side and the peripheral stumps of the gastroduodenal and right gastric arteries were drawn near to each other, and, in a manner of bridging them, a collateral arterial circulation was formed within the connective tissue. The status of this collateral circulation was varigated from the feeble development of only several filamentous branches to vigorous one including a great number of branches coursing in a bundle or reticularly. As shown in Table 3, development of the collateral circulation did not always correlate with the length of the survival period.

Table 3. Types and Degree of the Development of the Arterial Collateral Circulation after Interruption of the Hepatic Artery.

− No formation of collateral pathway
+ Slight collateral pathway
+ + Moderate Collateral circulation
+ + + Distinct Collateral circulation
+ + + + Most strong and vigorous formation and development of collateral pathway

In brancket are shown the courses which were noticed obviously.

		Type I					Type II					Type III	
		a.	b.	c.	d.	e.	α	α′	α″	β	β′	m	n
96	69	+					?	+	?	−	−	−	−
116	75	++	(a.b.)				+	++	+	++	++	−	+
109	81	++	(b.d.)				+	++	+	+	+	+	−
35	95	+					+	+	?	+	?	−	−
91	97	++					+	+	+	+	+	−	+
118	112	++	(a.b.d.)				+	++	+	+	+	−	−
105	127	+					++	++	+	+	+	−	−
87	133	+					+	+	++	+	+	+	−
84	185	+					+	++	+	+	+	+	−
32	201	+					+	+++	+	+	+	−	−
48	214	+					+	+	+	+	+	−	−
30	248	+					+	++	++	+	+	−	+
56	258	++	(a.b.c.d.e.)				++	++	+	+	++	−	−
53	266	+++					+	+	+	+	+	−	−
34	273	+++	(a.d.				+	+++	++	++	++	−	−
6	325	+++					+	++	+	+	+	−	−
2	339	++					++	++	+	+	+	−	−
9	356	+++	(e.)				+	++	+	+	+	−	−
3	367	++					+	++	+	+	+	−	−
18	551	++	(a.b.e.d.)				+++	++	+	+++	++	−	−

Fig. 18, 19, 20, 21, 22 and 23. The type I of the arterial collateral circulation in the hilum of the liver develops distinctly, especially in Figs. 21 and 23. with the many small arterial branches make network and anastomose intrahepatic arterial system.

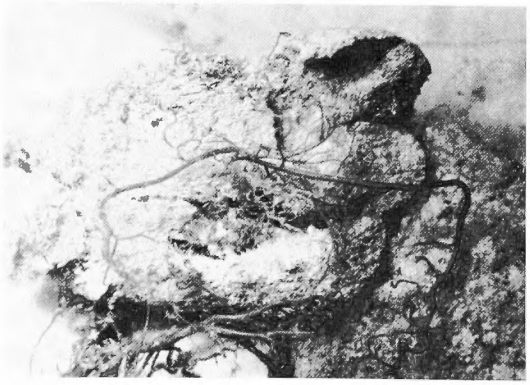


Fig. 18 (No. 116. 75 days)

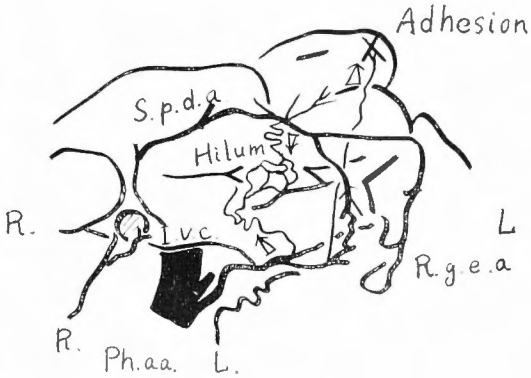
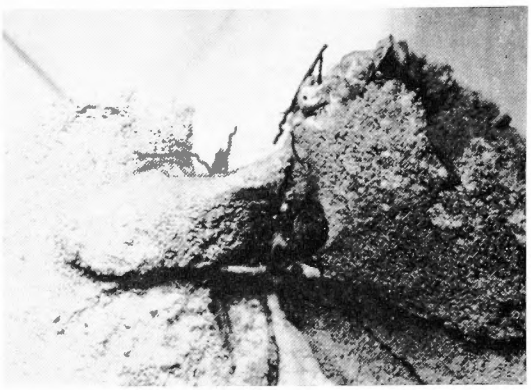


Fig. 19. (No. 109. 81 days)

Fig. 20. (No. 53. 273 days.)

Fig. 21. (No. 34. 266 days.)

Especially the highly potent development of the collateral circulation was noticed in the specimens of No. 116 (Fig. 18), No. 109 (Fig. 19), No. 53 (Fig. 20), No. 34 (Fig. 21), No. 6 (Fig. 22) and No. 9 (Fig. 23). The adhesion between the hilum of the liver and the proximal stump of the common hepatic artery did not take place and no collateral pathway was found in the stump.



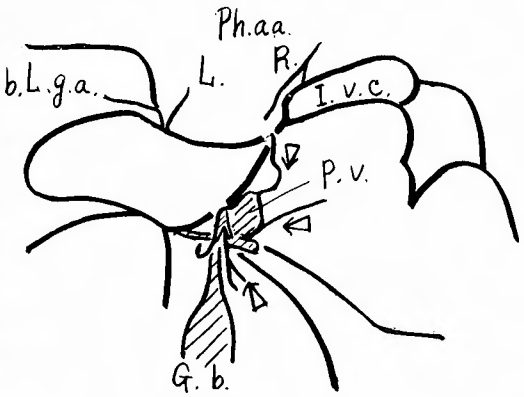


Fig. 22. (No. 6. 325 days.)

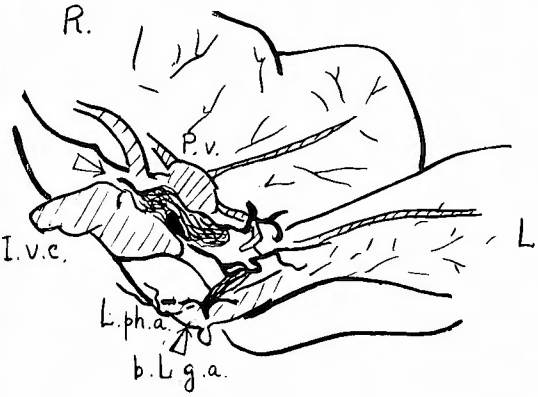


Fig. 23. (No. 9. 356 days.)

b. From the Diaphragmatic Surface of the Liver
(Type II, α, α', α'', β, β'.)

These are divided into 2 routes, one originating from the inferior phrenic artery of both sides and the left gastric artery which enter directly the proper hepatic artery running along the both sides of the caudate lobe and another originating from the inferior phrenic artery of both sides which drain into peripheral flow of the proper hepatic artery on the main branches of the hepatic vein of the each lobe.

1) The routes which reach directly the proper hepatic artery running along the both sides of the caudate lobe (Type II α, α', α'').

As already described before, the route of type II α' is the course which originates from a branch of the left inferior phrenic artery and runs between the left inferior lobe and caudate lobe around left side of cardia of the stomach and passes under the main branch of the left hepatic vein and then reaches the left proper hepatic artery, running parallel with the left branch of the portal vein which enters the caudate lobe.

The route of α'' is the course which comes out from a branch of the left gastric artery and finally reaches the left proper hepatic artery, either anastomosing with a branch of the left inferior phrenic artery around the cardia of the stomach or running along the same course as α' independently.

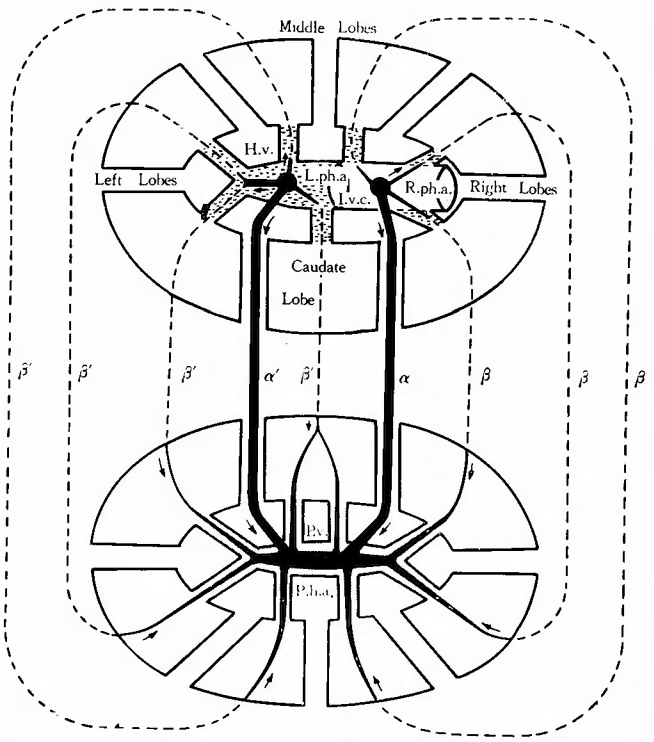
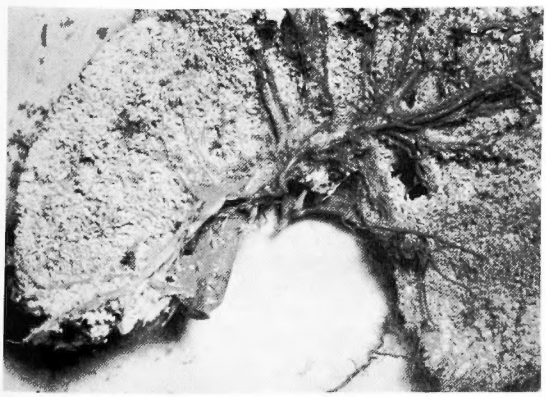


Fig. 24. Pattern of the arterial collateral pathways of the type II which anastomose with the intrahepatic arterial system.

I.v.c.	:	Inferior vena cava
H.v.	:	Hepatic vein
P.v.	:	Portal vein
P.h.a.	:	Proper hepatic artery
R.ph.a.	:	Right inferior phrenic artery
L.ph.a.	:	Left inferior phrenic artery

Fig. 25, 26, 27 and 28. The arterial collateral pathways of the type II α, and α'. Many branches ramified from the both inferior phernic arteries and the left gastric artery enter the liver at the right and left sides of the caudate lobe. In Figs. 25 and 27 the collateral pathway develops particularly vigorously. Several small arteries communicate with the left proper hepatic artery in bundel.



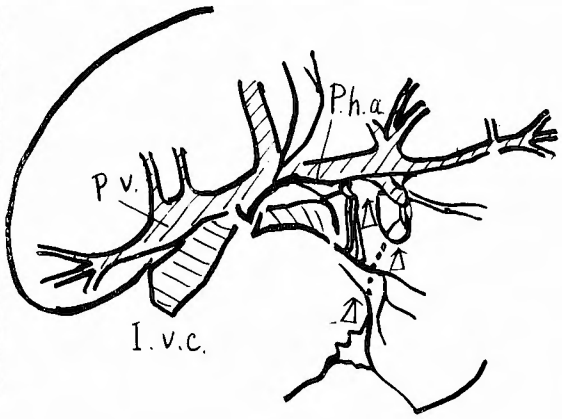


Fig. 25. (No. 32. 201 days.)

Fig. 26. (No. 56. 258 days.)

Fig. 27, a. (No. 34 266 days.)

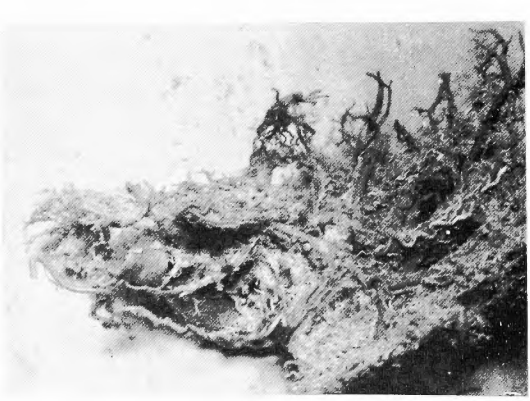


Fig. 27. b. (No. 34. 266 days.)

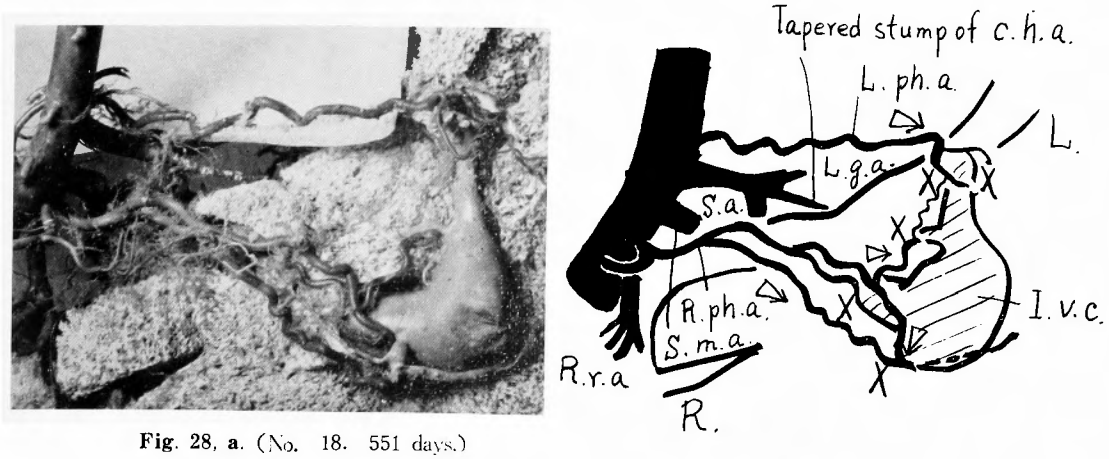


Fig. 28, a. (No. 18. 551 days.)

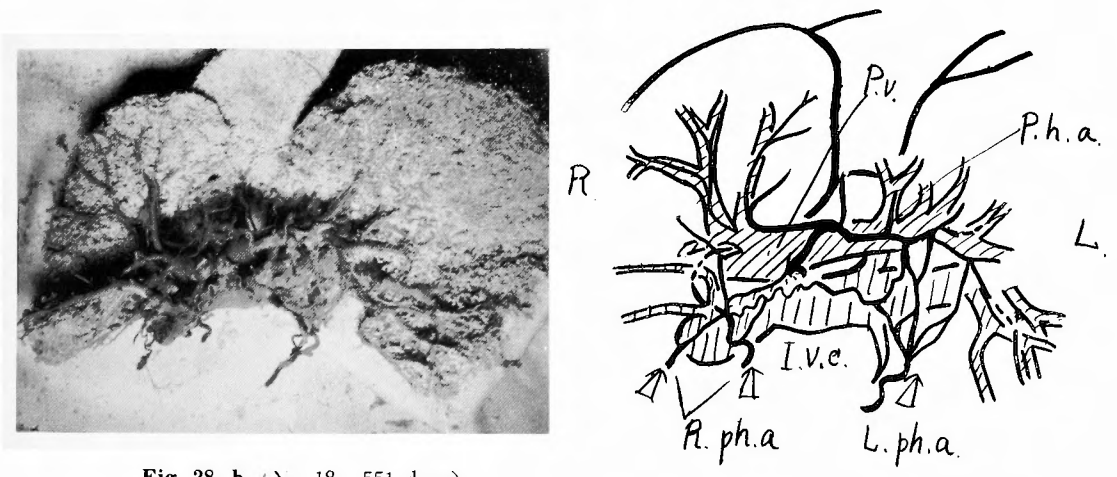


Fig. 28, b. (No. 18. 551 days.)

These two routes of α' and α'' have previously been pointed out by ISHIGURO.[17] Contrasting to these routes, the route α is the course which originates from a branch of the right inferior phrenic artery, ascends along the inferior vena cava, passes between the inferior vena cava and the caudate lobe, runs along the right side of the right branch of the portal vein which enters the caudate lobe and communicates with the right proper hepatic artery. (Fig. 24) These routes are observed most frequently and typically and they are most potent collaterals of the type II. The most remarkable development of these routes was noted in No. 32 (Fig. 25), No. 56 (Fig. 26), No. 34 (Fig. 27), and No. 18 (Fig. 28).

2) The routes which enter the liver along the branch of the hepatic vein of each lobe and communicate with the peripheral portion of the proper hepatic artery (Type II β, β').

These branches of the inferior phrenic artery of both sides run along the main branch of the hepatic vein in the left and along the superior surface of the inferior vena cava in the right, enter the space between each lobe and enter the parenchyma of the liver at the point of the main branches of each lobe, communicating with the peripheral

part of the intrahepatic arterial system. (Fig. 29) This group is not so potent as the former group of type II α, α' and α'', but distributed to every lobe of the liver communicating with the intrahepatic arterial system. (Fig. 17 & 24) These routes were distinctly noted in No. 116 (Fig. 30), No. 91 (Fig. 31), No. 34 (Fig. 32) and No. 18 (Fig. 33).

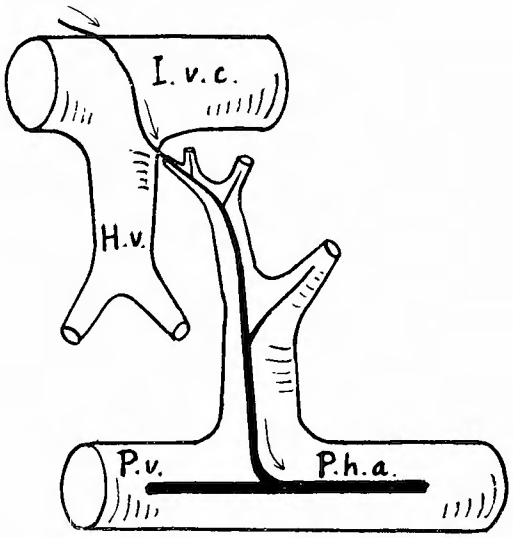


Fig. 29. Typical course of the type β and β′ at the portion where the collateteral pathway communicates with the peripheries of the each proper hepatic artery.
I.v.c. : Inferior vena cava H.v. : Hepatic vein
P.v. : Portal vein P.h.a. : Proper hepatic artery

Fig. 30, 31 32 and 33. The arterial collaterral pathways of the type II β and β′ develop distinctly.
In Fig. 33 the collateral pathways of this type anastomose with the peripheries of each proper hepatic artery at the surrounding area of each main branch of the hepatic vein.

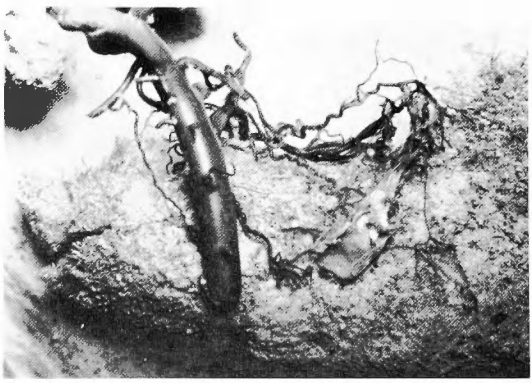
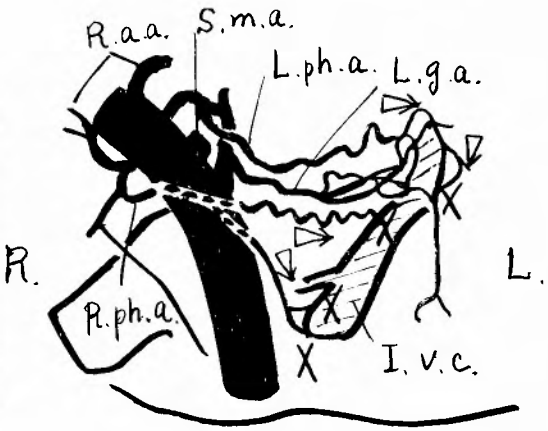


Fig. 30. (No. 116, 75 days.)



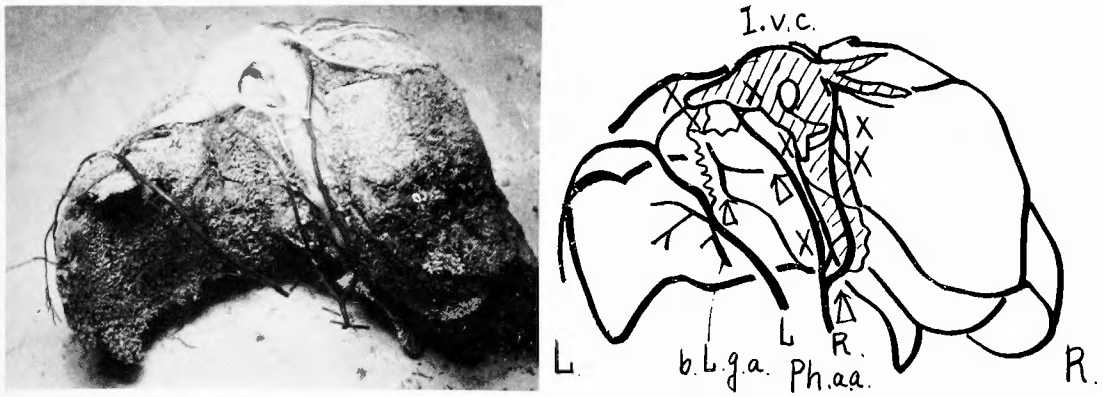


Fig. 31. (No. 91. 97 days.)

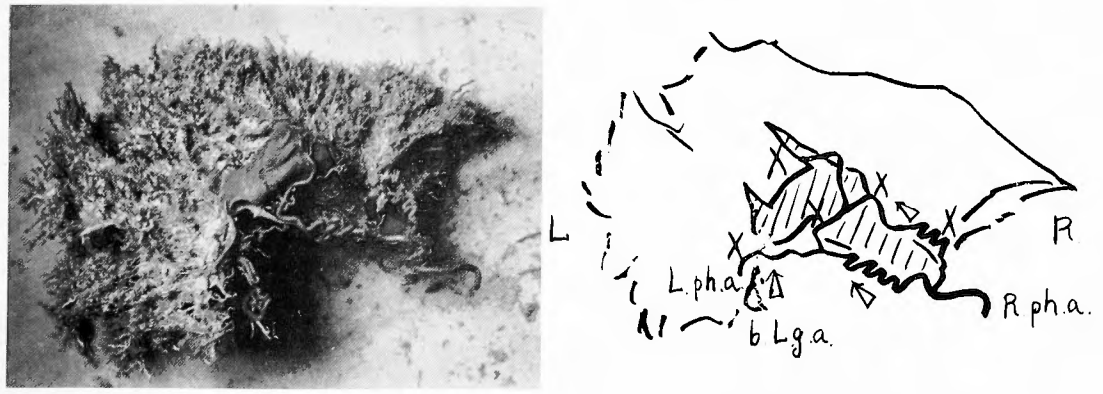


Fig. 32. (No. 31. 266 days.)

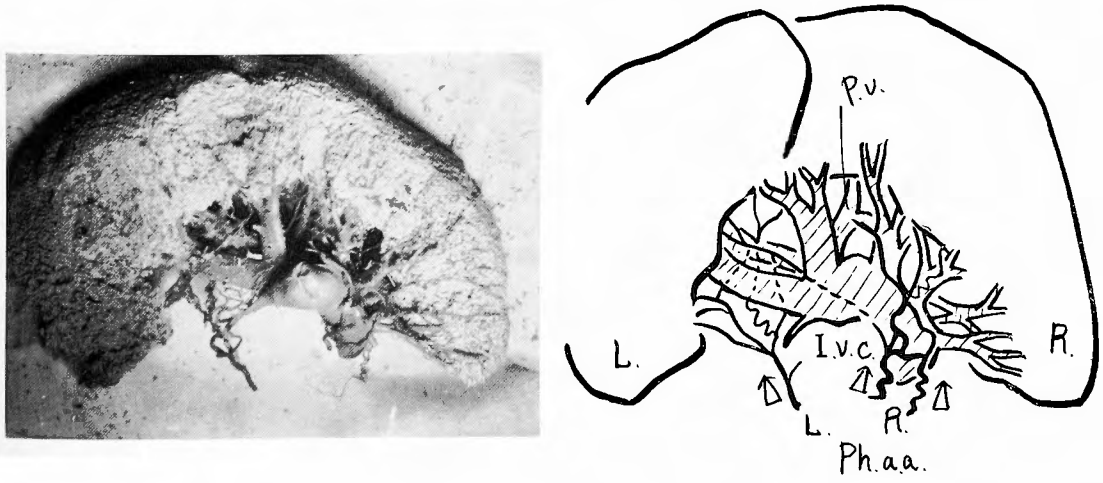
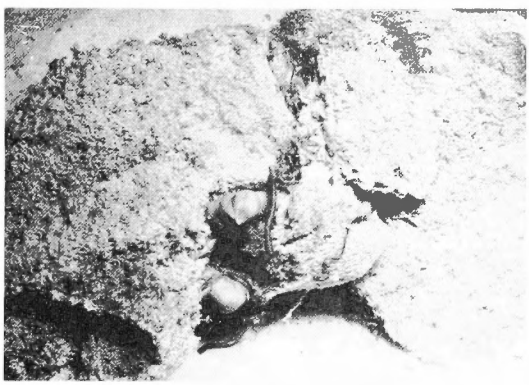


Fig. 33. (No. 18. 551 days.)

c. Other Collateral Arterial System (Type III m, n)

In a small number of cases, fine arterial branches, coursing between the hepatic surface and the adhered organs were observed and some of them were considered to be effective

Fig. 34. Collateral pathway of the type III n develops in the adhering tissue at the inferior surafce of the middle lobe.
Small arterial branches enter the liver parenchyma.



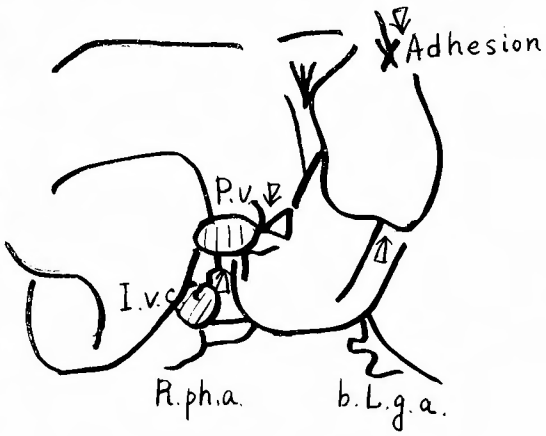


Fig. 34. (No. 31. 248 days.)

in arterial blood supply to the liver (No. 116, Fig. 18, No. 30, Fig. 34). The fine branches of the right renal artery were found in the right hepatorenal ligament and communicated with the intrahepatic arterial system. Most of these, however, are not capable of carrying any definite significance as the collateral arterial circulation entering the liver.

Although the development of the collateral arterial circulation is different case by case dogs on account of the length of survival period and individual difference, they may be classified into three types, I, II and III. It should be noted that all of these communicate with the intrahepatic arterial system most methodically and they supply systematically arterial blood to all the hepatic lobes.

v) *Comments*

The collateral arterial circulation develops gradually in the dogs surviving the interruption of the hepatic artery. Generally, 2 or 3 months after the operation the circulation becomes as potent as that in preoperative stage. Then it is interesting to note that the intrahepatic arterial system is uniformly distributed to all the hepatic lobes, corresponding with the distribution of the portal venous system in the same way as before the operation. The author believes from the facts mentioned below that the intrahepatic arterial system after the interruption of the hepatic artery is the preexisting one which is reactivated by the arterial blood supply from the collaterals.

1) The intrahepatic arterial system runs corresponding to the distribution of the portal venous system down to its peripheries and at the hilum of the liver site and shape of trifurcation of the arteries were anatomically unchanged as they once branched off from the common hepatic artery before the interruption.

2) Even immediately after the interruption of the hepatic arterial flow at the hilum as described in this paper, the fine branches of the left gastric artery and the inferior phrenic artery communicate with the intrahepatic arterial system, through which arterial blood, even though it is a small amount, may flow into the liver parenchyma. It is diffi-

cult to assume that the intrahepatic arterial system becomes completely empty and the occlusive process may happen in it.

Concerning the character and process of formation of types I and II which take leading parts in the formation of the collateral arterial pathways, type II of the collateral formed mainly from the inferior phrenic arteries, is assumed to have developed by a gradual hypertrophy or dilatation of these fine branches over an extended period of time, considering from the facts that (1) its pattern of anastomosis is constant and that (2), as mentioned before, a fine communication between a branch of the left inferior phrenic artery and the intrahepatic arterial system preexists before operation.

On the contrary, concerning type I of the collateral pathway, it may be considered that at least immediately after the operation the arterial system at the hilum of the liver was almost completely interrupted in the present experiment. The author believes that this collateral pathway is largely a development of the reticular vessels, newly formed and bridging over the stumps of each arteial cut end in the adhered connective tissue, and grown to connect the cut end of the hepatic side and that of the opposite side of the hepatic artery.

IV. SUMMARY AND DISCUSSION

The author examined the collateral arterial pathways in the dogs surviving for long the interruption of the main arterial supply to the liver. They entered the liver mainly from both the hilum of the liver and the diaphragatic surface of the liver and anastomosed with the intrahepatic arterial system and supplied sufficient arterial blood to the liver. The small arterial pathway had preexisted in the ligaments attached to the liver or between the liver and the diaphragm.

It should be noted, however, that in a critical period after major trunks in the hilum are interrupted, the amount of the arterial blood supplying the liver must be extremely small, as is easily seen from the anatomic relation between the intrahepatic and the surrounding arterial systems (ISHIGURO[18]). In addition, at least 2 or 3 months are required before the collateral arterial pathways are sufficiently developed. And the liver function in most cases of surviving dogs were in the normal range. In only 13.6 per cent of the total cases, temporary and quite slight impairment of the liver function was revealed for a short postoperative period of 1 or 2 weeks. Thus it seems that the liver is able to maintain its function, despite the decreased arterial blood supply.

From these results, it may be impossible to attribute the cause of a fatal liver necrosis in the early stage after the interruption of the hepatic artery merely to a decrease in the arterial blood entering the liver. It is also unlikely that the later development of the collateral arterial pathway can well prevent early necrosis of the liver.

V. CONCLUSION

The common hepatic, gastroduodenal and right gastric arteries, including the surrounding tissue except the portal vein and common bile duct were ligated and divided at the hilum of the liver in 113 dogs, in order to perform a complete interruption of the hepatic artery with concomitant administration of penicillin.

The pre- and postoperative examinations of the liver function and the blood were also carried out periodically, and plastic cast specimens of the vascular system of the liver including its neighboring organs were prepared and examined in both normal control and experimental long surviving dogs.

The results are as follows :

1) The mortality rate of interruption of the hepatic artery was as high as 49.5 per cent. The high mortality may be due to the great operative aggression in the hilar region at the time of hepatic arterial interruption.

2) The liver function was examined with five tests, comprising the sublimate reaction, MEULENGRACHT's icters index, KUNKEL's zinc sulphate test, B.S.P. test and TAKATA's reaction. In most cases of long survivals, remarkable changes could not be noted after the operation. Only slight impairment was noticed in 13.6 per cent of the cases and lasted for a week or two after the interruption.

3) As operative influences, red blood cell count, hemoglobin concentration and total serum protein decreased but they restored to preoperative levels within 2 to 3 months after the operation.

4) The collateral arterial circulation was formed gradually and 2 or 3 months after the interruption they provided to the liver as sufficient arterial blood supply as in the preoperative stage.

5) The collateral arterial pathways developed through regular routes of three types.

Type I. routes around the hilum of the liver

Type II. routes from the diaphragmatic surface of the liver

Type III. routes of other collateral system

Of these 3 types I and II played important roles.

The author gratefully acknowledges his gratitude to Prof. Dr. CHISATO ARAKI and Prpf. Dr. ICHIO HOMJO in the Kanazawa University for their kind guidances and encouragement during the present experiment.

REFERENCES

1) Harberer, H. : Experimentelle Unterbindung der Leberarterie. Arch. für Klin. Chir., **78**. 557, 1905
2) Markowitz, J., Rappaport, A. M. & Scott, A. C. : Prevention of Liver Necrosis Following Ligation of Hepatic Arteries. Proc. Soc. Exper. Biol. & Med., **70**, 305, 1949.
3) Fitts, W. T., Scott, R. & Mackie, J. : Effect of Antibiotics on Ligation of Hepatic Artery. Cites by Grant et al. Nov. 1950.
4) Ravdin, I. S. & Vars, H. M. : Factors Influencing Liver Injury and Liver Repair. Ann. Sur., **132**, 362, 1950.
5) Honjo, I. : Liver Cirrhosis and Hepatic Circulation. Jap. Clin. "Nihon Rinsho" in Jap., **15**, 1069, 1957.
6) Griadlay. J., Mann, F. C. & Bollman, J. L. : Effect of Occulsion of the Arterial Blood Supply to the Normal Liver. Arch. Surg., **62**, 806, 1951.
7) Grindlay, S. : Experimentally Produced Alteration of Hepatic Blood Flow. Arch. Surg., **66**, 562, 1953.
8) Eze, W. C. : Cause of Survival of Dogs without a Hepatic Artery. Arch. Surg., **65**, 684, 1952.
9) Laufman, H., Ross, A., Bernhard, V. M. Bourdeau, R. V., Furr. W. E. & Douglass. J. C. : Graded Hepatic Arterial Ligation in Experimental Ascites. Surg. Gyn. & Obst. **96**, 409, 1953.
10) Witter, J. A. & First, M. : Ligation of the Hepatic and Splenic Arteries for Advanced Periportal Cirrhosis. Surg., **33**, 663, 1953.
11) Popper, H. L., Jefferson, N. C. & Necheles, H. Survival of Dogs After Partial or Total Devascularization of the Liver. Ann. Surg., **140**, 93, 1954.
12) Tanturi, C., Swigart, L. & Canepa, J. : Prevention of Death from Experimental Ligation of the Liver

(Hepatic Proper) Branches of the Hepatic Artery. Surg. Gyn. & Obst., **91**, 680, 1950.
13) Urabe, H. : Experimental Study of the Interruption of the Arterial Blood Flow to the Liver. Arch. Jap. Chir., **28**, 1112, 1959.
14) Ishiguro, M. : Ligation of Hepatic Arteries and Collateral Arterial Circulation in Dogs. Arch. Jap. Chir., **28**, 2988, 1959.
15) Tsuchiya, R. : Experimental Study of Cirrhosis of the Liver. Arch. Jap. Chir., **28**, 1149, 1959.
16) Ikegami, K. : The Vasological. Study on the Gastro-enterostomy by Means of Plastic Injection Method. Arch. Jap. Chir., **28**, 470, 1959.
17) Ishiguro, M. : Ligation of Hepatic Arteries and Collateral Arterial Circulation in Dogs. Arch. Jap. Chir., **28**, 2971, 1959.
18) Ishiguro, M. : Ligation of Hepatic Arteries and Collateral Arterial Circulation in Dogs. Arch. Jap. Chir., **28**, 2986, 1959.

和文抄録

肝動脈遮断後長期生存犬の肝機能と動脈性副血行路に就いて

京都大学医学部外科教室第1講座（主任：荒木千里教授）

小　柴　孝　夫

犬に於いて肝動脈遮断後抗生物質投与により，死亡率が著明に減少するという事実は多くの学者により実証されて来たところである．肝動脈遮断により死亡する犬には必ず広汎な肝壊死を発生するが，此の肝壊死発生を防止する一次的な因子として抗生物質の果す役割に就いては異論のないところである．

而し肝動脈遮断後犬の生存を左右する二次的な原因に関しては今尚意見が鋭く対立している．即ち一方では術後形成される動脈性副血行路の多少に其の原因を求める学者が居り，他方では術後形成される副血行路は微々たるもので犬の生存を理由づけるに足らないとしその原因を他に求める人々がある．

私は此の問題点に立脚して肝動脈遮断後形成される動脈性副血行路が長期間に亘り如何なる様態を示すかを追究し，更に遮断犬の生存に如何なる意義を有するかを知るために，実験犬の肝臓並びに肝周辺の動脈，静脈，門脈系に合成樹脂を注入して各血管系の塑型標本を作成し，同時に術前後に亘り定期的に肝機能検査を実施し次の如き結果を得た．

(1)　ペニシリン投与下の肝門部に於ける肝流入動脈の徹底的遮断を意図して，総肝動脈．胃十二指腸動脈，右胃動脈を夫々の周囲結合組織を含めて結紮切断した．上記手術を113頭に実施し死亡率は49.5%に達した．

(2)　肝機能検査に昇汞反応，Meulengracht 黄疸指数 Kunkel 氏硫酸亜鉛試験，B.S.P. 試験，高田氏反応の5種に就いて行つたが，44例中僅か6例（13.6%）に極く軽度の肝機能障害を認めたに過ぎなかつた．しかも障害は術後1乃至2週間の短期間で一時的なものであつた．又肝機能検査と同時に血液検査（赤血球数，血色素濃度，血清総蛋白量）も実施した．これは手術侵襲により術後何れも減少したが2乃至3ヵ月で略術前値に恢復した．

(3)　動脈性副血行路に関しては，肝動脈遮断後最短69日最長551日に亘る長期生存犬20例の合成樹脂塑型標本に就いて観察し次の如き所見を得た．

夫々の犬によつて多少の個体差は免れないが，通常少くとも2乃至3ヵ月以後に於いて術前と略同程度に肝内に動脈血を供給し得る状態に達した．しかも副血行路は理路整然とした経路を通り肝内に侵入し，肝内動脈系と連絡して居り，定型的な分類をなすことが出来た．即ち肝門部を経て肝内に侵入する副血行路群（Ⅰ型）と肝横隔膜附着部より入る副血行路群（Ⅱ型）及び其の他の経路より肝臓と連絡する副血行路群（Ⅲ型）の3種類に大別し得た．Ⅰ型はその由来する動脈路により更に a. b. c. d. e. の5種類に細分しⅡ型は侵入する動脈の経路により更に α, α′, α″, β, β′, の5種類に分つことが出来，Ⅲ型は m, n, の2種類に分割した．以上の副血行路群の中，Ⅰ，Ⅱ型は殆んど全例に観察されしかも屢々最も著明な発達を来たして居り，肝内動脈血供給には此等副血行路が最も重要な役割を果していた．

(4)　肝動脈遮断後肝臓と周囲臓器を結ぶ動脈路が徐々に発達して術前同様の動脈血を肝臓に供給し肝動脈遮断に依る極度の動脈血の減少を代償し得るものと考えられる．しかし術後の犬の生存を左右する極く短期間に於いては肝臓に流入し得る動脈血は多少の個体差はあるにしろ，正常犬の肝内外の動脈系の検索からも又我が教室の石黒，占部の研究からも実証された如く微々たるものにすぎない．従つて肝臓えの動脈血による酸素供給も術前に比し極度に減少しているものと考えられる．しかも副血行路が充分発達するには少くとも2乃至3ヵ月を要する．更に私の実験によれば生存犬の肝機能は大多数正常値を保ち術後短期間といえども少数例に軽度の障害を一時的に見るのみである．即ち肝臓は相当の乏酸素環境下にあつても良くその機能を営み得るものと推測される．

以上の結果から肝動脈結紮遮断により発生する致命的な肝壊死の原因を肝臓に流入する動脈血の減少にのみ帰することはむつかしいし，又動脈性副血行路形成の多少をもつて説明することは尚困難である．